2-'4-(2-HYDROXYMETHYL-PHENYLAMINO)-PIPERIDIN-1-YL!-N-(9H-CARBAZOL-3-YL)-ACETAMINE DERIVATIVES AND RELATED COMPOUNDS AS NEUROPEPTIDE Y5 (NPY5) LIGANDS FOR THE TREATMENT OF OBESITY

The present invention relates to 1,4-disubstituted piperidine compounds of general formula (I), methods for their preparation, medicaments comprising these compounds as well as their use for the preparation of a medicament for the treatment of humans or animals.

Neuropeptide Y (NPY), first isolated in porcine brain extracts (Tatemoto et. al. Nature 1982, 296, 659), is a 36-aminoacid peptide belonging to the family of pancreatic polypeptides, and is one of the most abundant peptides in the brain and in the central nervous system. Several studies suggest that NPY plays a significant role in cognitive function regulation, e. g. memory (Flood J. F. et. al. Brain Res. 1987, 421, 280; Redrobe J. P. et. Al. Brain Res. 1999, 848, 153), and in the development of anxiety (Heilig M. et. al. Reg. Peptides 1992, 41, 61) and depression (Heilig M. et. al. Eur. J. Pharmacol. 1988, 147, 465).

Moreover, NPY is also distributed in the peripheral system and some studies suggest that it is involved in hypertensive (Michel M. C: et. al. J. Hypertens. 1995, 13, 385), and analgesic (Gehlert D. R. Life Sci. 1994, 55, 551) processes, among others.

The endogenous proteins that constitute NPY-binding receptors have been widely studied. Several have been cloned and expressed. At present, six different receptor subtypes, named Y1 to Y6, are recognized (Hispkind P. A. et. al. Annu. Rep. Med. Chem. 1996, 31, 1; Grundemar L. et. al. TIPS Reviews., 15, 153, 1994). Each NPY receptor subtype is generally associated to a different biological activity.

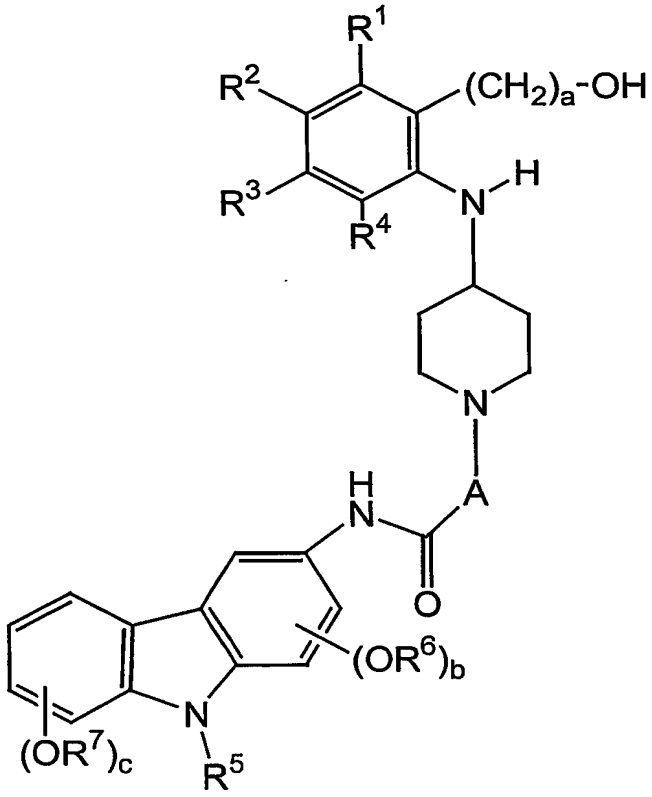
The most recently identified receptor is Y5 (Hu et. al. J. Biol. Chem. 1996, 271, 26315). Since there is ample evidence that the Y5 receptor has a unique pharmacological profile compared to the other receptor subtypes, it was initially expected that the Y5 receptor might be a suitable target for the treatment of food intake related disorders such as obesity. This attitude has changed and it is now the common opinion among those skilled in the art that the Y5 receptor in general is not a suitable target for a treatment of food intake related disorders such as obesity. This

change in attitude may be attributed to the fact that the compounds with affinity for the NPY-5 receptor tested so far were not orally active, see also Current Opinion in Investigational Drugs 2003, 4, 1198; Diabetes Vol. 51, August 2002, 2441 and International Journal of Obesity 2004, 28, 628.

Thus, it was an object of the present invention to provide novel compounds that are suitable in particular as active substances in medicaments, preferably in medicaments for the regulation of neuropeptide Y receptors, particularly preferably of neuropeptide Y 5 (NPY5) receptor, for the regulation of food intake and for the prophylaxis and/or treatment of food intake related disorders such as obesity, anorexia, cachexia, bulimia or type II (non insulin dependent) diabetes.

Surprisingly, it has been found that the 1,4-disubstituted piperidine compounds of general formula (I) given below have affinity for neuropeptide Y receptors, in particular for neuropeptide Y 5 (NPY5) receptors. Moreover, the compounds according to the present invention have surprisingly been found to show significant appetite suppressing effects.

Therefore, in one of its aspects the present invention relates to 1,4-disubstituted piperidine compounds of general formula (I),



wherein

a represents 0, 1, 2, 3 or 4,

b represents 0, 1, 2 or 3,

c represents 0, 1, 2, 3 or 4,

R^1, R^2, R^3, R^4 are each independently selected from the group consisting of hydrogen; halogen; -CN; -NO_2; -OR^8; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic radical, which may be bonded via an alkylene

group; or an optionally at least mono-substituted aryl- or heteroaryl radical, which may be bonded via an alkylene group and/or which may be condensed with an optionally at least mono-substituted, saturated or unsaturated mono- or bicyclic ring system,

R^5 represents hydrogen, a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, or a saturated or unsaturated, optionally at least mono-substituted cycloaliphatic radical,

R^6, R^7 and R^8, identical or different, each represent hydrogen or a prodrug-moiety,

A represents a $-CH_2-$ or $-CH_2-CH_2-$ group,

optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, its racemate or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or a salt, preferably a physiologically acceptable salt thereof, or a corresponding solvate, respectively.

Preferred are 1,4-disubstituted piperidine compounds of general formula (I) given above, wherein

a represents 0, 1, 2, 3 or 4,

b represents 0, 1, 2 or 3,

c represents 0, 1, 2, 3 or 4,

R^1, R^2, R^3, R^4 are each independently selected from the group consisting of H; F; Cl; Br; -CN; $-NO_2$; $-OR^8$; a linear or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6}-aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8}-cycloaliphatic radical, which may be bonded via a C_{1-3}-alkylene group; or an optionally at least mono-substituted aryl- or heteroaryl radical, which may be bonded

via a C_{1-3}-alkylene group and/or which may be condensed with an optionally at least mono-substituted, saturated or unsaturated mono- or bicyclic ring system,

R^5 represents hydrogen, a linear or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6}-aliphatic radical, or a saturated or unsaturated, optionally at least mono-substituted C_{3-8}-cycloaliphatic radical,

R^6, R^7 and R^8, identical or different, each represent hydrogen or a prodrug-moiety,

A represents a $-CH_2-$ or $-CH_2-CH_2-$ group,

optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, its racemate or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or a salt, preferably a physiologically acceptable salt thereof, or a corresponding solvate, respectively.

A prodrug moiety in the sense of the present invention is a moiety that will give rise to a pharmacologically active metabolite of the respective compound of general formula I in vivo.

Suitable prodrug moieties, methods for their preparation, methods for their introduction into a starting compound to give a compound of general formula I as defined above as well as methods for determination of the metabolite formed in vivo are well known to those skilled in the art, e.g. from the textbooks of Krogsgaard-Larsen, Povl, "A textbook of drug design and development" Harwood Academic (ISBN 3-7186-5100-9) and from Bernard Testa and Joachim B. Mayer, "Hydrolysis in drug and prodrug metabolism: Chemistry, biochemistry and enzymology, Wiley-VCH, 2003, Weinheim (ISBN-3-906390-25-X). The respective parts of the literature description are hereby incorporated by reference and form part of the present disclosure.

A mono- or bicyclic ring system according to the present invention means a mono- or bicyclic hydrocarbon ring system that may be saturated, unsaturated or aromatic. If the ring system is bicyclic, each of its different rings may show a different degree of saturation, i.e. it may be saturated, unsaturated or aromatic. Optionally each of the rings of the mono- or bicyclic ring system may contain one or more heteroatoms as ring members, which may be identical or different and which can preferably be selected from the group consisting of N, O, S and P, more preferably be selected from the group consisting of N, O and S. Said mono- or bicyclic ring-system may preferably contain 0, 1, 2 or 3 heteroatoms chosen from the afore mentioned group, preferably it contains 0 or 1 heteroatoms chosen from the afore mentioned group. The rings of the mono- or bicyclic ring system are preferably 5- or 6-membered.

Those skilled in the art understand that the term "condensed" indicates that the condensed rings share more than one atom. The terms "annulated" or "fused" may also be used for this type of bonding.

If one or more of the residues R^1-R^5 represents an aliphatic radical, which is substituted by one or more substituents, unless defined otherwise, each of these substituents may preferably be selected from the group consisting of hydroxy, halogen, branched or linear C_{1-4}-alkoxy, branched or linear C_{1-4}-perfluoroalkoxy, branched or linear C_{1-4}-perfluoroalkyl, amino, carboxy, amido, cyano, nitro, $-SO_2NH_2$, $-CO-C_{1-4}$-alkyl, $-SO-C_{1-4}$-alkyl, $-SO_2-C_{1-4}$-alkyl, $-NH-SO_2-C_{1-4}$-alkyl , wherein the C_{1-4}-alkyl may in each case be branched or linear, an unsubstituted or at least mono-substituted phenyl or naphthyl radical and an unsubstituted or at least mono-substituted furanyl-, thienyl-, pyrrolyl-, imidazolyl-, pyrazolyl-, pyridinyl-, pyrimidinyl-, quinolinyl- and isoquinolinyl radical, more preferably be selected from the group consisting of hydroxy, F, Cl, Br, methoxy, ethoxy, CF_3 and an unsubstituted phenyl radical. If any one of these substituents itself is at least mono-substituted, said substituents may preferably be selected from the group consisting of F, Cl, methyl and methoxy. Preferably the substituted alkyl radical may be substituted with 1, 2, 3, 4 or 5, more preferably with 1, 2 or 3 of the afore mentioned substituents.

If one or more of the residues R^1-R^5 represents or comprises a cycloaliphatic radical, which is substituted by one or more substituents, unless defined otherwise, each of these substituents may preferably be selected from the group consisting of hydroxy, halogen, branched or linear C_{1-4}-alkyl, branched or linear C_{1-4}-alkoxy, branched or linear C_{1-4}-perfluoroalkoxy, phenoxy, benzoyl, cyclohexyl, branched or linear C_{1-4}-perfluoroalkyl, $-NR^AR^B$ wherein R^A, R^B are each independently selected from the group consisting of H, a branched or linear C_{1-4}-alkyl-radical, $-CH_2-CH_2-OH$ and phenyl, carboxy, amido, cyano, nitro, $-SO_2NH_2$, - $CO-C_{1-4}$-alkyl, $-CO-OC_{1-4}$-alkyl, $-SO-C_{1-4}$-alkyl, $-SO_2-C_{1-4}$-alkyl, $-NH-SO_2-C_{1-4}$-alkyl, wherein C_{1-4}-alkyl may in each case be branched or linear, unsubstituted or at least mono-substituted phenyl or naphthyl and an unsubstituted or at least mono-substituted furanyl-, thienyl-, pyrrolyl-, imidazolyl-, pyrazolyl-, pyridinyl-, pyrimidinyl-, quinolinyl- and isoquinolinyl radical, more preferably be selected from the group consisting of hydroxy, F, Cl, Br, methyl, ethyl, methoxy, ethoxy, benzoyl, phenoxy, cyclohexyl, $-CF_3$, $-CO-CH_3$, $-CO-OCH_3$, $-NR^AR^B$ wherein R^A, R^B are each independently selected from the group consisting of H, a branched or linear C_{1-4}-alkyl-radical, $-CH_2-CH_2-OH$ and phenyl, and an unsubstituted phenyl radical. If any one of these substituents itself is at least mono-substituted, said substituents may preferably be selected from the group consisting of F, Cl, methyl and methoxy. Preferably the substituted cycloaliphatic radical may be substituted with 1, 2, 3, 4 or 5, more preferably with 1, 2 or 3 of the afore mentioned substituents.

If one or more of the residues R^1-R^4 comprises a mono- or bicycyclic ring system, which is substituted by one or more substituents, unless defined otherwise, each of these substituents may preferably be selected from the group consisting of hydroxy, halogen, branched or linear C_{1-4}-alkyl, branched or linear C_{1-4}-alkoxy, branched or linear C_{1-4}-perfluoroalkoxy, branched or linear C_{1-4}-perfluoroalkyl, amino, carboxy, amido, cyano, keto, nitro, $-SO_2NH_2$, $-CO-C_{1-4}$-alkyl, $-SO-C_{1-4}$-alkyl, $-SO_2-C_{1-4}$-alkyl, - $NH-SO_2-C_{1-4}$-alkyl, wherein C_{1-4}-alkyl may be branched or linear, an unsubstituted or at least mono-substituted phenyl or naphthyl radical and unsubstituted or at least mono-substituted furanyl-, thienyl-, pyrrolyl-, imidazolyl-, pyrazolyl-, pyridinyl-, pyrimidinyl-, quinolinyl- and isoquinolinyl, more preferably from the group consisting of hydroxy, F, Cl, Br, methyl, ethyl, methoxy, ethoxy, CF_3, keto (=O), cyano and an unsubstituted phenyl radical. If any one of these substituents itself is at least mono-substituted, said substituents may preferably be selected from the group consisting of

F, Cl, methyl and methoxy. Preferably the substituted mono- or bicycyclic ringsystem may be substituted with 1, 2, 3, 4 or 5, more preferably with 1, 2 or 3 of the afore mentioned substituents.

If one or more of the residues R^1-R^4 represents or comprises an aryl radical, which is substituted by one or more substituents, unless defined otherwise, each of these substituents may preferably be selected from the group consisting of hydroxy, halogen, branched or linear C_{1-4}-alkoxy, branched or linear C_{1-4}-alkyl, branched or linear C_{1-4}-perfluoroalkoxy, unsubstituted or at least mono-substituted phenoxy, unsubstituted or at least mono-substituted benzoyl, cyclohexyl, branched or linear C_{1-4}-perfluoroalkyl, NR^AR^B wherein R^A, R^B are each independently selected from the group consisting of H, a branched or linear C_{1-4}-alkyl-radical, $-CH_2-CH_2-OH$ and phenyl, carboxy, amido, cyano, -C(H)(OH)(phenyl), $-C(H)(OH)(CH_3)$, nitro, $-SO_2NH_2$, $-CO-C_{1-4}$-alkyl, $-CO-OC_{1-4}$-alkyl, $-SO-C_{1-4}$-alkyl, $-SO_2-C_{1-4}$-alkyl, $-NH-SO_2-C_{1-4}$-alkyl, wherein C_{1-4}-alkyl may be branched or linear, an unsubstituted or at least mono-substituted phenyl or naphthyl radical and unsubstituted or at least mono-substituted furanyl-, thienyl-, pyrrolyl-, imidazolyl-, pyrazolyl-, pyridinyl-, pyrimidinyl-, quinolinyl- and isoquinolinyl radical, more preferably be selected from the group consisting of hydroxy, F, Cl, Br, methyl, ethyl, cyano, -C(H)(OH)(phenyl), $-C(H)(OH)(CH_3)$, methoxy, ethoxy, unsubstituted or at least mono-substituted benzoyl, unsubstituted or at least mono-substituted phenoxy, cyclohexyl, CF_3, $-CO-CH_3$, $-CO-OCH_3$, $-NR^AR^B$ wherein R^A, R^B are each independently selected from the group consisting of H, a branched or linear C_{1-4}-alkyl-radical, $-CH_2-CH_2-OH$ and phenyl, and an unsubstituted phenyl radical. If any of these substituents itself is at least mono-substituted, said substituents may preferably be selected from the group consisting of F, Cl, methyl and methoxy. Preferably the substituted aryl radical may be substituted with 1, 2, 3, 4 or 5, more preferably with 1, 2 or 3 of the afore mentioned substituents.

If one or more of the residues R^1-R^4 represents or comprises a heteroaryl radical, which is substituted by one or more substituents, unless defined otherwise, each of these substituents may preferably be selected from the group consisting of hydroxy, halogen, branched or linear C_{1-4}-alkoxy, branched or linear C_{1-4}-alkyl, branched or linear C_{1-4}-perfluoroalkoxy, unsubstituted or at least mono-substituted phenoxy, unsubstituted or at least mono-substituted benzoyl, cyclohexyl, branched or linear C_{1-}

$_{4}$-perfluoroalkyl, NR^AR^B wherein R^A, R^B are each independently selected from the group consisting of H, a branched or linear C_{1-4}-alkyl-radical, $-CH_2-CH_2-OH$ and phenyl, carboxy, amido, cyano, nitro, -C(H)(OH)(phenyl), $-C(H)(OH)(CH_3)$, $-SO_2NH_2$, $-CO-C_{1-4}$-alkyl, $-CO-OC_{1-4}$-alkyl, $SO-C_{1-4}$-alkyl, SO_2-C_{1-4}-alkyl, $-NH-SO_2-C_{1-4}$-alkyl, wherein C_{1-4}-alkyl may be branched or linear, an unsubstituted or at least mono-substituted phenyl or naphthyl radical and an unsubstituted or at least mono-substituted furanyl-, thienyl-, pyrrolyl-, imidazolyl-, pyrazolyl-, pyridinyl-, pyrimidinyl-, quinolinyl- and isoquinolinyl radical, more preferably be selected from the group consisting of hydroxy, F, Cl, Br, methyl, ethyl, cyano, methoxy, ethoxy, unsubstituted or at least mono-substituted benzoyl, unsubstituted or at least mono-substituted phenoxy, cyclohexyl, CF_3, -C(H)(OH)(phenyl), $-C(H)(OH)(CH_3)$, $-CO-CH_3$, $-CO-OCH_3$, $-NR^AR^B$ wherein R^A, R^B are each independently selected from the group consisting of H, a branched or linear C_{1-4}-alkyl-radical, $-CH_2-CH_2-OH$ and phenyl, and an unsubstituted phenyl radical. If any one of these substituents itself is at least mono-substituted, said substituents may preferably be selected from the group consisting of F, Cl, methyl and methoxy. Preferably the substituted heteroaryl radical may be substituted with 1, 2, 3, 4 or 5, more preferably with 1, 2 or 3 of the afore mentioned substituents.

Alkylene groups according to the present invention may preferably be selected from the group consisting of $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-CH_2-$, $-CH_2-CH(CH_3)-CH_2-$, $-CH_2-CH_2-CH(CH_3)-$, $-C(CH_3)_2-CH_2-CH_2-$, $-CH_2-CH_2-C(CH_3)_2-$ and $-CH_2-CH_2-CH_2-CH_2$.

If one or more of the residues R^1-R^5 represents or comprises a cycloaliphatic radical, which contains one or more heteroatoms as ring members, unless defined otherwise, each of these heteroatoms may preferably be selected from the group consisting of N, O, S and P, more preferably from the group consisting of N, O and S. Said cycloaliphatic radical may preferably contain 0, 1, 2 or 3 heteroatoms chosen from the afore mentioned group, more preferably it contains 0 or 1 heteroatoms chosen from the afore mentioned group.

If one or more of the residues R^1-R^4 represents or comprises an heteroaryl radical, which contains one or more heteroatoms as ring members, unless defined otherwise, each of these heteroatoms may preferably be selected from the group consisting of N, O, S and P, more preferably from the group consisting of N, O and S. Said heteroaryl radical may preferably contain 1, 2 or 3 heteroatoms chosen from the afore mentioned group, preferably it contains 1 or 2 heteroatoms chosen from the afore mentioned group.

Preferred are compounds of general formula (I), wherein R^1, R^2, R^3, R^4 are each independently selected from the group consisting of H; F; Cl; Br; -CN; -NO_2; -OR^8; a linear or branched, optionally at least mono-substituted C_{1-4}-alkyl radical, a saturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_5- or C_6- cycloaliphatic radical, which may be bonded via an optionally at least mono-substituted C_1- or C_2-alkylene group;

more preferably R^1, R^2, R^3, R^4 are each independently selected from the group consisting of H; F; Cl; Br; -CN; -NO_2; -CH_3; -CH_2CH_3; -CHF_2; -CH_2F; -CF_3; -CF_2CF_3; OR^8; cyclopentyl and cyclohexyl,

even more preferably R^1, R^2, R^3, R^4 are each independently selected from the group consisting of H; F; Cl; Br, CH_3 and OR^8 and R^5-R^8, A, a, b and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein R^5 represents H or a linear or branched C_{1-6} alkyl radical,

more preferably R^5 represents H or an alkyl radical selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl and R^1-R^4, R^6-R^8, A, a, b and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their

racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein R^6, R^7 and R^8, identical or different, each represent H or a prodrug-moiety selected from the group consisting of

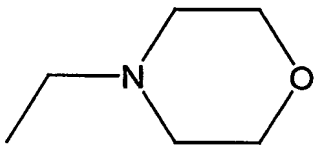
linear or branched C_{1-3}-alkyl,

a $P(=O)(OR^9)_2$ group, wherein R^9 represents a linear or branched C_{1-4}-alkyl radical,

a $-(C=O)-O-R^{10}$ group, wherein R^{10} represents a linear or branched C_{1-5}-alkyl radical,

a $-(C=O)-NH-R^{11}$ group, wherein R^{11} represents a phenyl group, which is mono-substituted with a linear or branched C_{1-3} alkyl radical,

a $-(C=O)-R^{12}$ group, wherein R^{12} represents a phenyl group, which is mono-substituted with a $-O-(C=O)-C_{1-3}$-alkyl radical, an $-CH_2-N(C_{1-4}\text{-alkyl})_2$ group or a



group

and R^1-R^5, A, a, b and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein R^6, R^7 and R^8, identical or different, each represent H or a prodrug-moiety selected from the group consisting of

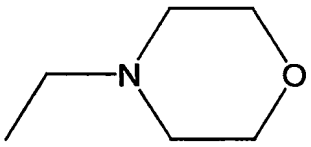
linear or branched C_{1-3}-alkyl,

a $P(=O)(OR^9)_2$ group, wherein R^9 represents methyl or ethyl,

a $-(C=O)-O-R^{10}$ group, wherein R^{10} represents an alkyl radical selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl,

a $-(C=O)-NH-R^{11}$ group, wherein R^{11} represents a phenyl group, which is mono-substituted with methyl or ethyl,

a $-(C=O)-R^{12}$ group, wherein R^{12} represents a phenyl group, which is mono-substituted with $-O-(C=O)-C_{1-3}$-alkyl radical in the ortho position or with an $-CH_2-N(C_{1-4}\text{-alkyl})_2$ in the meta or para position or with a



group

in the meta or para position and R^1-R^5, A, a, b and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein R^6, R^7 and R^8 each represent hydrogen and R^1-R^5, A, a, b and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein A represents a $-CH_2-$ group and R^1-R^4, R^5, R^6-R^8, a, b and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein a represents 1, 2 or 3, more preferably 1 or 2, even more preferably 1 and R^1-R^4, R^5, R^6-R^8, A, b and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein b represents 0, 1 or 2, more preferably 0 or 1 and R^1-R^4, R^5, R^6-R^8, A, a and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein c represents 0, 1 or 2, preferably 0 or 1 and R^1-R^4, R^5, R^6-R^8, A, a and b have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein at least one of the substituents R^1, R^2, R^3 and R^4 represents $-OR^8$ and the other substituents of R^1, R^2, R^3 and R^4 and R^5, R^6-R^8, A, a, b and c have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein one or two of the substituents R^1, R^2, R^3 and R^4 represent $-OR^8$ and the other substituents of R^1, R^2, R^3 and R^4 and R^5, R^6-R^8, A, a and b have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Also preferred are compounds of general formula (I), wherein one or two of the substituents R^1, R^2, R^3 and R^4 represent $-OR^8$ and b and c each represent 0,

more peferably one of the substituents R^1, R^2, R^3 and R^4 represents $-OR^8$ and b and c each represent 0 and in each case the other substituents of R^1, R^2, R^3 and R^4 and R^5, R^6-R^8, A and a have the meaning given above, optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or salts, preferably physiologically acceptable salts thereof, or corresponding solvates, respectively.

Most preferred are 1,4-disubstituted piperidine compounds of general formula (I) selected from the group consisting of:

[1] 2-[4-(3-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide,

[2] 2-[4-(4-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide,

[3] 2-[4-(5-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide,

[4] 2-[4-(6-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide,

[5] 2-[4-(3-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide,

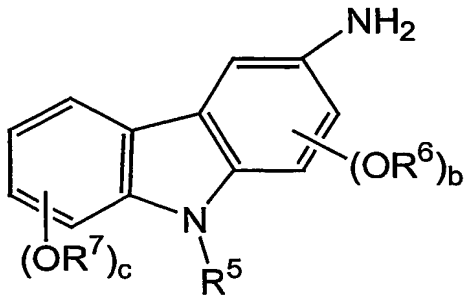
[6] 2-[4-(4-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide,

[7] 2-[4-(5-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide and

[8] 2-[4-(6-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide,

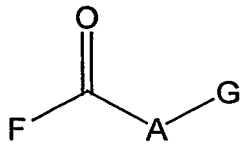
optionally in form of a salt, preferably a physiologically acceptable salt, more preferably in form of a physiologically acceptable acid addition salt, most preferably a hydrochloride salt, or a corresponding solvate.

In a further aspect the present invention also provides a process for the preparation of 1,4-disubstituted piperidine compounds of general formula (I), wherein at least one compound of general formula (II),



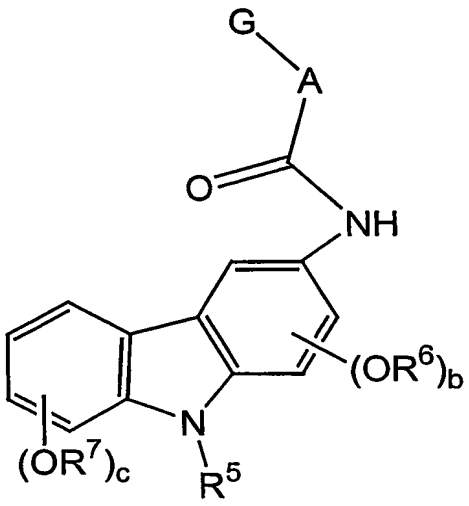
(II),

wherein R^5, R^6 and R^7, b and c have the meaning given above; is reacted with at least one compound of general formula (III),



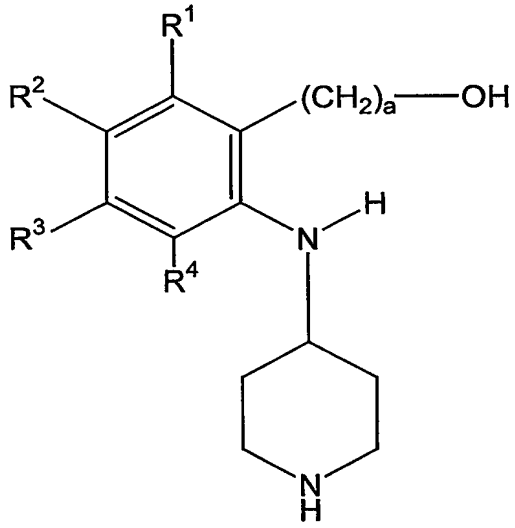
(III)

wherein A has the meaning according given above, F represents halogen, preferably chlorine, hydroxy or an O-acyl group and G represents halogen, preferably chlorine, in a suitable reaction medium and preferably in the presence of at least one base and/or at least one auxiliary agent, and reacting the so obtained compound of general (IV)



(IV),

wherein A, G, R^5, R^6 and R^7, b and c have the above defined meaning, with at least one piperidine compound of general formula (V) and/or a salt, preferably a hydrochloride salt thereof,

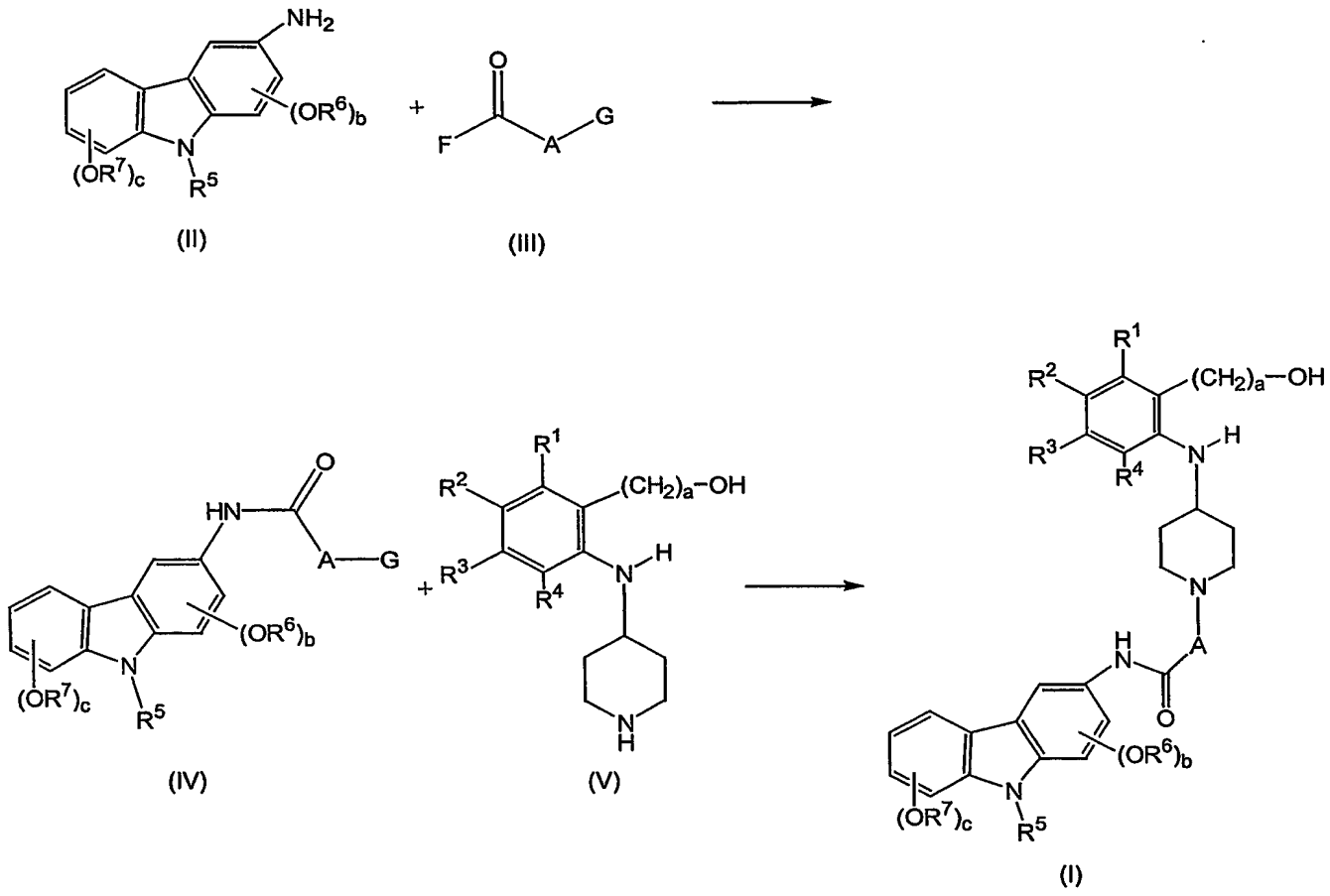


(V),

wherein R^1 to R^4 and a have the meaning given above, in a suitable reaction medium, optionally in the presence of at least one base and/or at least one auxiliary agent, to yield a compound of general formula (I), wherein R^1-R^7, A, a, b and c have the meaning as given above.

According to the invention, the process may be illustrated as an example by the following reaction scheme 1:

Scheme 1:



wherein R^1-R^7, A, a, b and c have the meaning as given above.

Suitable reaction media are e.g. organic solvents, such as ethers, preferably diethyl ether, dioxane, tetrahydrofurane, dimethyl glycol ether, or alcohols, e.g. methanol, ethanol, propanol, isopropanol, butanol, isobutanol, tert-butanol, or hydrocarbons, preferably benzene, toluene, xylene, hexane, cyclohexane, petroleum ether, or halogenated hydrocarbons, e.g. dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, trichloroethylene, chlorobenzene or/and other solvents, preferably ethyl acetate, triethylamine, pyridine, dimethylsulfoxide, dimethylformamide, hexamethylphosphoramide, acetonitril, acetone or nitromethane,

are included. Mixtures based one or more of the aforementioned solvents may also be used.

Bases that may be used in the processes according to the present invention are generally organic or inorganic bases, preferably alkali metal hydroxides, e.g. sodium hydroxide or potassium hydroxide, or obtained from other metals such as barium hydroxide or different carbonates, preferably potassium carbonate, sodium carbonate, calcium carbonate, or alkoxides, e.g. sodium methoxide, potassium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide or potassium tert-butoxide, or organic amines, preferably triethylamine, diisopropyethylamine or heterocycles, e.g. 1,4-diazabicyclo[2.2.2] octane, 1,8-diazabicyclo[5.4.0]undec-7-ene pyridine, diamino pyridine, dimethylaminopyridine, methylpiperidine or morpholine. Alkali metals and their hydrides such as sodium or its hydrides, e.g. sodium hydride, may also be used. Mixtures based one or more of the aforementioned bases may also be used.

The above mentioned bases may be used for the process as auxiliary agents, when appropriate. Other suitable auxiliary agents for the above mentioned reactions are, for example, dehydrating agents like carbodiimides, e.g. diisopropylcarbodiimide, cyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, or carbonylic compounds, e.g. carbonyldiimidazol or compounds like isobutylchloroformiate or methansulfonyl chloride, among others. These reagents are generally used in amounts from 0.5 to 5 mol versus 1 mol of the corresponding reactands. These bases are generally used in amounts from 0.05 to 10 mol versus 1 mol of the corresponding reactands.

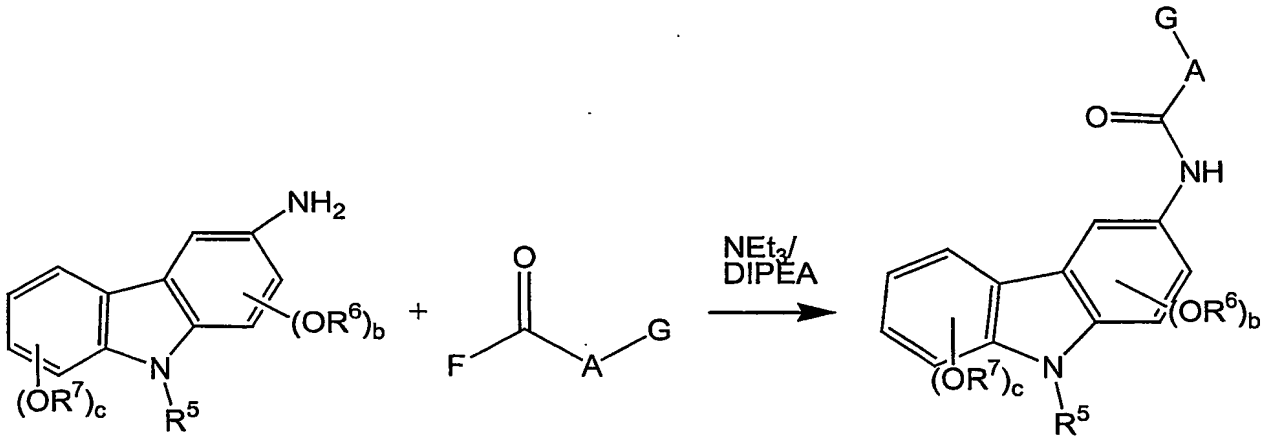
During some of the synthetic reactions described or while preparing the compounds of general formulas (I), (II), (III), (IV), and (V) the protection of sensitive groups or of reagents may be necessary and/or desirable. This can be performed by using conventional protective groups like those described in the literature, e.g. in Protective groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991. The protective groups may also be eliminated as convenient by means well-known to

those skilled in the art. The respective parts of the literature description are hereby incorporated by reference and form part of the present disclosure.

The compounds of general formulas (II), (III), (IV) and (V) are either commercially available or can be produced according to methods known to those skilled in the art. The reaction of compounds of general formulas (IV) and (V) to yield 1,4-disubstituted piperidine compounds of general formula (I) may also be facilitated by conventional methods known to those skilled in the art.

The compounds of general formula (IV) are commercially available or may be produced by conventional methods known to those skilled in the art. In particular, the respective compound of general formula (II) may be reacted with chloroacetyl chloride or the respective compound of general formula (III) in the presence of an organic reaction medium, preferably dichloromethane and a base, preferably triethylamine and/or diisopropylethylamine as depicted in scheme 2.

Scheme 2:

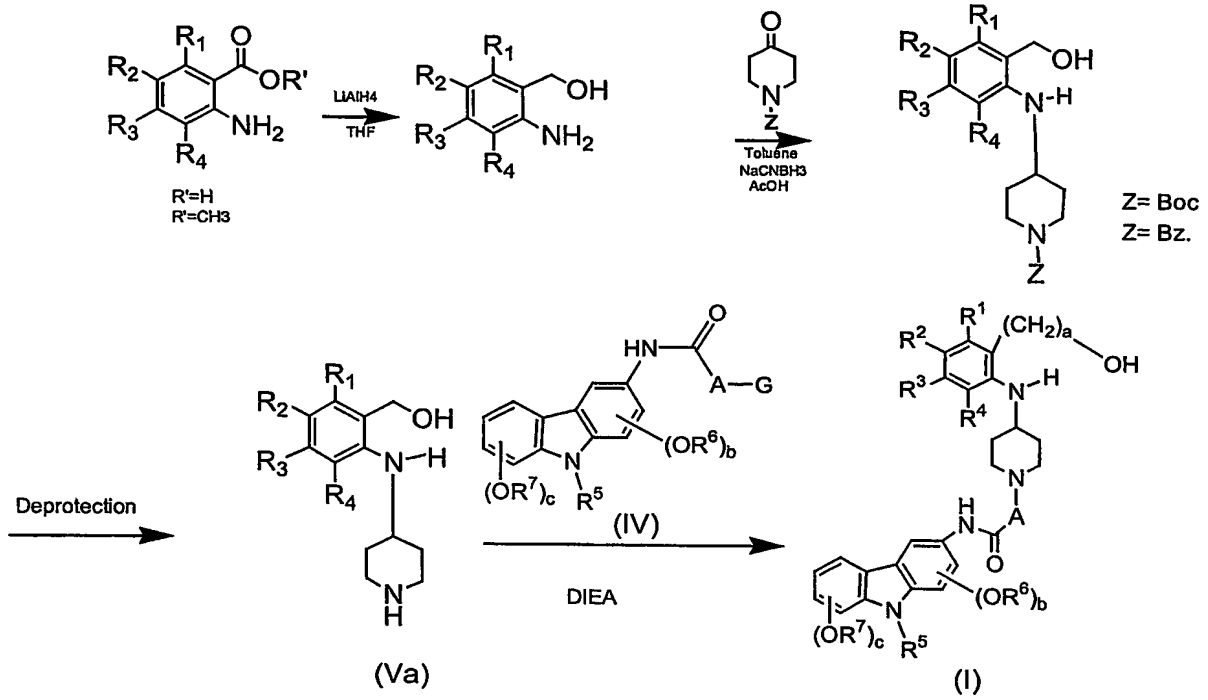


(II) (III) (IV)

DIEA = Diisoproylethylamin

The preparation of compounds of general formula (Va), wherein R^1-R^4 have the meaning as given above and their use for the preparation of compounds of general formula (I) is illustrated in scheme 3 given below:

Scheme 3



DIEA = Diisopropylethylamin, Boc = tert-Butoxycarbonyl, Bz = Benzyloxycarbonyl

In a further aspect the present invention also provides a process for the preparation of salts of 1,4-disubstituted piperidine compounds of general formula (I), wherein at least one compound of general formula (I) is reacted with an inorganic and/or organic acid, preferably in the presence of a suitable reaction medium. Suitable reaction media are the ones given above. Suitable inorganic acids are for example hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, nitric acid, suitable organic acids are e.g. citric acid, maleic acid, fumaric acid, tartaric acid, or derivatives thereof, such as p-toluenesulfonic acid, methanesulfonic acid or camphersulfonic acid.

In yet a further aspect the present invention also provides a process for the preparation of salts of 1,4-disubstituted piperidine compounds of general formula (I), wherein at least one compound of general formula (I) having at least one acidic group is reacted with one or more suitable bases, preferably in the presence of a suitable reaction medium. Suitable bases are e.g. hydroxides, carbonates or alkoxides, which include suitable cations, derived e.g. from alkaline metals, alkaline

earth metals or organic cations, e.g. $[NH_nR_{4-n}]^+$, wherein n is 0, 1, 2, 3 or 4 and R represents a branched or unbranched C_{1-4}-alkyl-radical.

Solvates, preferably hydrates, of the 1,4-disubstituted piperidine compounds of general formula (I), or corresponding stereoisomers, or corresponding salts may also be obtained by standard procedures known to those skilled in the art.

If the 1,4-disubstituted piperidine compounds of general formula (I) are obtained in form of a mixture of stereoisomers, particularly enantiomers or diastereomers, said mixtures may be separated by standard procedures known to those skilled in the art, e.g. chromatographic methods or crystallization with chiral reagents.

The purification and isolation of the 1,4-disubstituted piperidine compounds of general formula (I) or a corresponding stereoisomer, or a corresponding salt, or corresponding solvate respectively, if required, may be carried out by conventional methods known to those skilled in the art, e.g. chromatographic methods or recrystallization.

The 1,4-disubstituted piperidine compounds of general formula (I), their stereoisomers or the respective salts or solvates are toxicologically acceptable and are therefore suitable as pharmaceutical active substances for the preparation of medicaments.

Surprisingly, it has been found that the 1,4-disubstituted piperidine compounds of general formula (I) have affinity for neuropeptide Y receptors, in particular for neuropeptide Y 5 (NPY5) receptors. Moreover, the compounds according to the present invention have surprisingly been found to show significant appetite suppressing effects in rats, if administered orally or parenterally. It is particularly suprising that the compounds of general formula (I) are pharmacologically active, if administered orally.

The present invention therefore also provides for a medicament comprising at least one 1,4-disubstituted piperidine compound of general formula (I), optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, its racemate or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or a physiologically acceptable salt thereof, or a solvate, respectively, and optionally one or more pharmaceutically acceptable adjuvants.

Furthermore, the present invention also provides for a pharmaceutical composition comprising at least one 1,4-disubstituted piperidine compound of general formula (I), optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, its racemate or in form of a mixture of at least two of its stereoisomers in any mixing ratio, or a physiologically acceptable salt thereof, or a solvate, respectively, and optionally one or more pharmaceutically acceptable adjuvants, which is not yet formulated into a medicament.

Preferably the medicament is suitable for the regulation of neuropeptide Y receptors, preferably of neuropeptide Y 5 (NPY5) receptor, for the regulation of appetite, for the regulation of body weight, for the prophylaxis and/or treatment of disorders related to food ingestion, preferably selected from the group consisting of obesity, anorexia, cachexia, bulimia, diabetes (particularly type (II) diabetes), for the improvement of cognition (cognitive enhancement); for the prophylaxis and/or treatment of disorders of the peripheral nervous system; for the prophylaxis and/or treatment of disorders of the central nervous system; for the prophylaxis and/or treatment of arthritis; for the prophylaxis and/or treatment of epilepsy; for the prophylaxis and/or treatment of anxiety; for the prophylaxis and/or treatment of depression; for the prophylaxis and/or treatment of cognitive disorders, more preferably memory disorders; for the prophylaxis and/or treatment of cardiovascular diseases; for the prophylaxis and/or treatment of pain; for the prophylaxis and/or treatment of hypertensive syndrom; for the prophylaxis and/or treatment of inflammatory diseases; for the prophylaxis and/or treatment of immune diseases; for the prophylaxis and/or treatment of panic attacks; and for the prophylaxis and/or treatment of bipolar disorders.

The present invention also provides for the use of at least one 1,4-disubstituted piperidine compound of general formula (I), optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, its racemate or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or a physiologically acceptable salt thereof, or a solvate, respectively, for the manufacture of a medicament for the regulation of neuropeptide Y receptors, preferably of neuropeptide Y 5 (NPY5) receptor, for the regulation of appetite, for the regulation of body weight, for the prophylaxis and/or treatment of disorders related to food ingestion, preferably selected from the group consisting of obesity, anorexia, cachexia, bulimia, diabetes (particularly type (II) diabetes), for the improvement of cognition (cognitive enhancement); for the prophylaxis and/or treatment of disorders of the peripheral nervous system; for the prophylaxis and/or treatment of disorders of the central nervous system; for the prophylaxis and/or treatment of arthritis; for the prophylaxis and/or treatment of epilepsy; for the prophylaxis and/or treatment of anxiety; for the prophylaxis and/or treatment of depression; for the prophylaxis and/or treatment of cognitive disorders, preferably memory disorders; for the prophylaxis and/or treatment of cardiovascular diseases; for the prophylaxis and/or treatment of pain; for the prophylaxis and/or treatment of hypertensive syndrom; for the prophylaxis and/or treatment of inflammatory diseases; for the prophylaxis and/or treatment of immune diseases; for the prophylaxis and/or treatment of panic attacks; and for the prophylaxis and/or treatment of bipolar disorders.

The medicament according to the present invention is particularly suitable for the administration to mammals, including humans. The medicament can be administered to patients of all ages, namely children, adolescents and adults. The composition of the medicament may vary depending on the route of administration.

The preparation of the corresponding pharmaceutical compositions as well as the formulated medicaments can be carried out by means of conventional methods known in the prior art, for example, from the indices of "Pharmaceutics: The Science of Dosage Forms", Second Edition, Aulton, M.E. (ED. Churchill Livingstone, Edinburgh (2002)); "Encyclopedia of Pharmaceutical Technology", Second Edition, Swarbrick, J. and Boylan, J.C. (Eds.), Marcel Dekker, Inc. New York (2002); "Modern

Pharmaceutics", Fourth Edition, Banker G.S. and Rhodes C.T. (Eds.) Marcel Dekker, Inc. New York (2002), and "The Theory and Practice of Industrial Pharmacy", Lachman L., Lieberman H. and Kanig J. (Eds.), Lea & Febiger, Philadelphia (1986). The respective literature descriptions are incorporated as a reference and are part of this disclosure.

The pharmaceutical compositions, as well as the formulated medicaments prepared according to the present invention, can, in addition to at least one compound of general formula (I), optionally in the form of one of its stereoisomers, preferably enantiomers or diastereomers, its racemate, or in form of a mixture of at least two of its stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or a corresponding physiologically acceptable salt thereof or a corresponding solvate thereof, comprise other conventional auxiliary substances known in the prior art, preferably excipients, fillers, solvents, diluents, dyes, coating agents, matrix forming agents and/or binders.

As the skilled persons in the art also knows, the choice of the auxiliary substances and the amounts thereof depend on the intended administration route, for example, rectal, intravenous, intraperitoneal, intramuscular, intranasal, oral, buccal or topical.

Medicaments suitable for oral administration are, for example, tablets, coated tablets, capsules or multiparticulates, preferably granules or pellets, optionally compressed into tablets, filled in capsules or suspended in suitable liquids.

Medicaments suitable for parenteral, topical or inhalatory administration may preferably be chosen from the group consisting of solutions, suspensions, quickly reconstitutable dry preparations and also sprays.

Medicaments suitable for oral or percutaneous use can release the compounds of general formula (I) in a sustained manner, the preparation of these sustained release medicaments generally being known in the prior art.

Suitable sustained release forms, as well as the materials and methods for the preparation thereof, are known in the prior art, for example from the indices of "Modified-Release Drug Delivery Technology", Rathbone, J.JI, Hadgraft, J. and Roberts, M.S. (Eds.), Marcel Dekker, Inc., New York (2002); "Handbook of Pharmaceutical Controlled Release Technology", Wise, D.L. (Ed.), Marcel Dekker, Inc. New York (2000); "Controlled Drug Delivery", Vol. I, Basic Concepts, Bruck, S.D. (Ed.), CRD Press, Inc., Boca Raton (1983), and by Takada, K. and Yoshikawa, H., "Oral Drug Delivery", Encyclopedia of Controlled Drug Delivery, Mathiowitz, E. (Ed.), John Wiley & Sons, Inc., New York (1999), Vol. 2, 728-742; Fix, J., "Oral drug delivery, small intestine and colon", Encyclopedia of Controlled Drug Delivery, Mathiowitz, E. (Ed.), John Wiley & Sons, Inc., New York (1999), Vol. 2, 698-728. The respective literature references are incorporated by reference and form part of the disclosure.

The medicament of the present invention may also have at least one enteric coating, which dissolves according to the pH. As a result of this coating, the medicament may pass through the stomach without dissolving, and the compounds of general formula I are only released in the intestinal tract. The enteric coating preferably dissolves at a pH of between 5 and 7.5. The materials and methods suitable for preparing enteric coatings are also known in the prior art.

The above mentioned compositions include preferably 1 to 60 % by weight of one or more of the 1,4-disubstituted piperidine compound of general formula (I), optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, its racemate or in form of a mixture of at least two of its stereoisomers in any mixing ratio, or a physiologically acceptable salt thereof, or a solvate, respectively, and 40 to 99 % by weight of the appropriate pharmaceutical vehicle(s).

The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, weight or degree of illness and so forth. The daily dosage for mammals including humans usally ranges from 1 milligram to 5000 milligram, preferably 1 to 3000 mg, more preferably 1 to 2000 mg of substance to be administered during one or several intakes.

Pharmacological Methods:

Neuropeptide Y_5 Receptor binding studies:

The methods used for membrane preparation and binding are similar to those described by Y. Hu, B. T. Bloomquist et al. in Y. Hu, B. T. Bloomquist et al., The Journal of Biological Chemistry, 1996, 271, 26315-26319 with modifications. Said literature description is herewith incorporated by reference and forms part of the disclosure. Cells C6 were transfected with the rat Y5 receptor. The cells were grown under standard culture conditions in 150 cm^2 dishes and they were harvested using a rubber scraper and 10 ml PBS. The cells from five dishes were collected and centrifuged 2.500 g for 5 min (4°C). The pellet was washed by resuspending in 3 ml buffer (Tris-HCl 10 mM, pH 7.4), homogenized using a Potter S homogenizer, 10 strokes at 600 rpm and centrifuged 48.000 g for 20 min (4°C). The pellet was resuspended in 8 ml membrane buffer (Tris-HCl 25 mM, NaCl 120 mM, KCl 5 mM, KH_2PO_4 1,2 mM, $CaCl_2$ 2,5 mM, $MgSO_4$ 1,2 mM, BSA 0,15 mg/ml, Bacitracine 0,5 mg/ml, pH 7,4) and rehomogenized using the Potter S, 10 strokes at 600 rpm. The protein concentration in the incubation was 40 µg/ml. The radioligand was [^{125}I]-PYY (100 pM) in a total incubation volume of 200 µl. Following incubation at 25°C for 2 h, the reaction was stopped by addition of 5 ml ice-cold buffer (Tris-HCl 25 mM, NaCl 120 mM, KCl 5 mM, KH_2PO_4 1,2 mM, $CaCl_2$ 2,5 mM, $MgSO_4$ 1,2 mM, pH 7,4) and rapid filtration in a Harvester Brandell Cell using filters (Schleicher & Schuell GF 3362) pretreated for two hours with 0,5% polyethyleneimine. Filters were washed one time with 5 ml ice-cold buffer. The filters were placed into plastic scintilation vials and 5 ml scintilation cocktail Ecoscint H were added. The quantity of radioactivity present was determined in a Wallac Winspectral 1414 counter. Non specific binding was determined in the presence of 1 µM de pNPY. All binding assays were done in triplicate.

Behavioural model (Food intake measurements)

In this test the effect of the compounds of general formula (I) on food and water intake in male rats can be determined.

Animals:

128 male Sprague Dawley Rats (aged 6 weeks, approximately 190 g; obtained from Charles River, Germany) were used. The rats arrived 32 at a time. Upon arrival they were be housed 3 per cage for one week and subsequently transferred to individual cages mounted with feeders containing powdered chow. During the single housing period, rats were handled daily to accustom them to the injection procedure. From the arrival date, rats are kept under a 12/12 L/D cycle lights on at 0300 and in temperature and humidity controlled rooms.

Treatment groups and randomization

Two weeks after the arrival, the rats were transferred to MANI Feedwin cages and randomized into 4 weight-matched groups, that is 8 rats per group. Rats had ad libitum access to a powdered diet (Atromin rodent chow, C.Petersen Ringsted) and tap water. In addition, body weight was monitored daily.

Rats were subjected to a maximum of 4 injections, each separated by at least 3 days. If carry over effects were still present at that time injections were postponed further. All compounds were administered in three doses: 5, 30 and 60 mg/kg. All compounds were administered p.o. by gavage (gavage volume of 5-8 ml/kg, determined by the solubility of the compound).

Group 1 Vehicle
Group 2 testing compound (I) 5 mg/kg
Group 3 testing compound (I) 30 mg/kg
Group 4 testing compound (I) 60 mg/kg

Experimental procedure

For 2 days prior to transfer to the MANI Feedwin cages, in addition to the daily handling procedure rats were gavaged daily with vehicle. Baseline food intake (digital balance) and lick counts were monitored from day 1 to day 3. First day of injection was day 3. Prior to lights out (14.30 PM) the rats were administered the testing compound and vehicle by gavage. Food intake (digital balance) and water intake (registered as lick counts) were monitored online every 5^{th} minute for 48 hours following the time of injection or until the effect of the drug had worn off.

Testing compounds (I) with significant appetite suppressing effects, i. e. effective compounds, at any of the following time points 1, 4, 6, 12, 18, 24, 48 h after the injection were re-administered to the same group of rats in a randomized manner so that no rat received the same dosage twice.

In addition, the following analysis was carried out for effective testing compounds:

- Locomotor activity (consecutive beam streaks) analyzed for 48 hours following administration of the testing compounds at the same time as food intake was registered

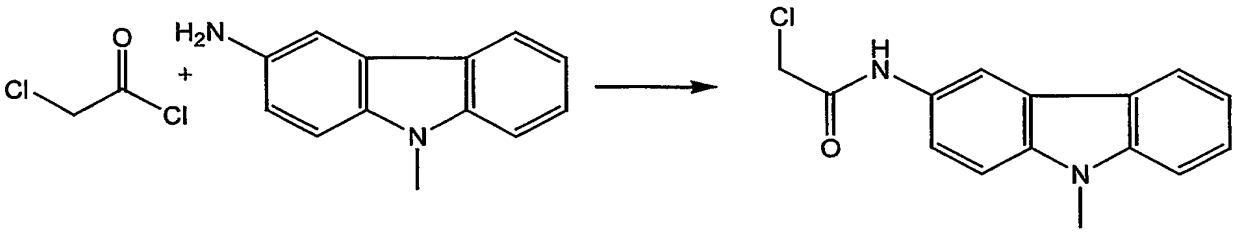
- Meal microstructure analysis based on the food and licking data from the experiment in 5 minutes intervals. The meal size, the meal duration, the interval between two meals and the meal numbers was analyzed during the first 24 hours after administration.

The following examples are given to illustrate the present invention, but they do not limit the scope of the present invention.

Examples:

EXAMPLE A :

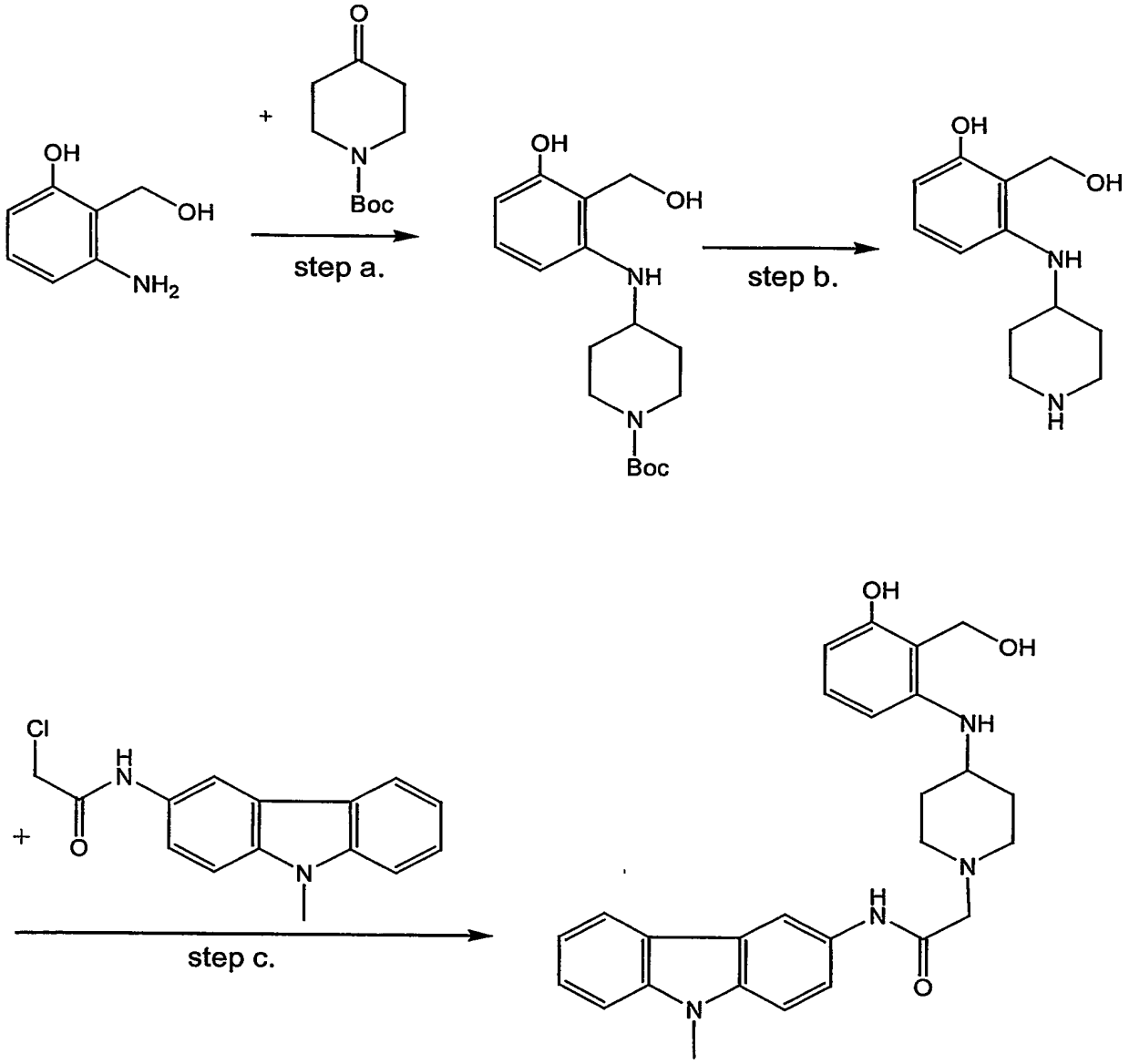
2-Chloro-N-(9-methyl-9H-carbazol-3-yl)-acetamide



A solution of 3-amino-9-methyl-9H-carbazol (10 mmols), triethylamine (2.07 ml, 15 mmols), in 25 ml of dried dichloromethane, is cooled to 10° C and a solution of chloroacetyl chloride (10.5 mmoles) in 10 ml of dried dichloromethane is then added drop by drop. The resulting mixture is kept stirring for 1 hour at room temperature overnight.The mixture is washed with 2x30 ml of water, dried over sodium sulfate and evaporated to give 2,5 g of 2-Chloro-N-(9-methyl-9H-carbazol-3-yl)-acetamide.

EXAMPLE 1 :

2-[4-(3-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide



step a)

A solution of 1-(*tert*-butyloxycarbonyl)-4-piperidinone (0.01 mol), 3-Amino-2-hydroxymethyl-phenol (0.011 mol) and acetic acid (1.4 ml, 0.022 mol) in dried toluene (50 mL) were heated to reflux, removing the water by means of azeotropic distillation with a Dean-Stark, over 30 hours. Then, the mixture was cooled and concentrated under vacuum to the half of the volume. $NaBH_3CN$ (2 g, 0.032 mol) and dried THF (30 mL) is added to a resulting solution.

Afterwards, acetic acid (1 mL, 0.017 mol) was added slowly and the reaction mixture was stirred at room temperature over 24 hours. The mixture was concentrated under vacuum and the residue was dissolved in ethyl acetate (75 mL), washed with a saturated $NaHCO_3$ (4 x 25 mL) and a saturated NaCl solution (25 mL), dried and evaporated to dryness. This raw material was used in the following step.

step b)

A solution of 3.2 g of the raw material obtained in the previous step a) in 40 mL of dried ethyl acetate, was cooled to 0°C. Then a 5 M hydrogen chloride solution in ethyl ether (40 mL) was added and the resulting mixture was kept at 0°C over 4 hours. The solvent was evaporated and the residue was suspended in water and was alcalinized with sodium hydroxide, and was extracted with chloroform (3 x 20 mL), the combined organic extracts were washed with water, dried over sodium sulfate and evaporated. The raw material was purified via column cromatography by eluting with chloroform:methanol 9:1 (vol/vol). In this way 1,3 g of a yellow solid were obtained.

step c)

A mixture of 3-N-(4-Amino-piperidin)-2-hydroxymethyl-phenol (4.70 mmol), 2-Chloro-N-(9-methyl-9H-carbazol-3-yl)-acetamide (5 mmol) and K_2CO_3 (1380 mg, 10 mmol) in DMF (40 mL) was stirred at 10°C for 2 hours and then at room temperature overnight. The reaction mixture was added to 50 mL water and 100 mL ethyl acetate, the organic phase was decanted and washed with water (3 x 50 mL),

dried over sodium sulfate and a 2.8 M hydrogen chloride solution in absolute ethanol (1.80 mL) was added, to precipitate the hydrochloride, which was filtered off and washed with ethyl acetate to obtain the compound 2-[4-(3-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide with a yield of 70%.

The compounds according to the following examples 2-8 have been prepared as described above for the compound according to example 1.

Example 2:

2-[4-(4-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide

Example 3:

2-[4-(5-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide

Example 4:

2-[4-(6-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-methyl-9H-carbazol-3-yl)-acetamide

Example 5:

2-[4-(3-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide

Example 6:

2-[4-(4-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide

Example 7:

2-[4-(5-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide

Example 8:

2-[4-(6-Hydroxy-2-hydroxymethyl-phenylamino)-piperidin-1-yl]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide.